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D E C I S I O N
of 27 April 2004

Case Number: W 0001/04 - 3.3.2

Application Number: PCT/EP 03/01594

Publication Number: WO 03/070236

IPC: A61K 31/415

Language of the proceedings: EN

Title of invention:
Tricyclic Pyrozole derivatives, process for their preposition and their use as antitumor agent

Applicant:
Pharmacia Italia S.P.A.

Opponent:
-

Headword:
Pyrozole derivatives/PHARMACIA ITALIA S.P.A.

Relevant legal provisions:
PCT Art. 17(3)a
PCT R. 40

Keyword:
"Splitting of Markush formula not based on structural considerations only"

Decisions cited:
W 0003/93

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: W 0001/04

International Application No. PCT/EP 03/01594

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 27 April 2004

Applicant: PHARMACIA ITALIA S.P.A.
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I-20152 Milano (IT)

Representative: PHARMACIA ITALA S.P.A.
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I-20014 Nervino (MI) (IT)

Decision under appeal: **Protest according to Rule 40.2(c) of the Patent Cooperation Treaty made by the applicants against the invitation (payment of additional fees) of the European Patent Office (International Searching Authority) dated 23 December 2003 .**

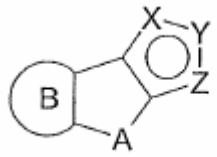
Composition of the Board:

Chairman: U. Oswald
Members: J. Riolo
B. Günzel

Summary of Facts and Submissions

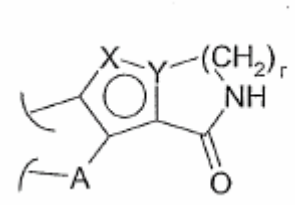
I. The applicant filed an international patent application, No. PCT/EP 03/01594, comprising a set of 31 claims, the independents claims of which read as follows:

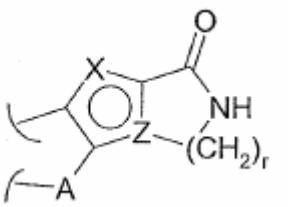
"**1.** A method for treating diseases caused by and/or associated with an altered protein kinase activity which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I)



(I)

wherein
X, Y and **Z,** being part of an aromatic ring are selected, each independently, from the group consisting of N, NR_1, S, O and CR_1;
R_1 is selected from the group consisting of hydrido, lower alkyl, perfluorinated lower allyl, heterocyclyl, CN, CO_2R', $COCF_3$, COR', CONR'R", NR'R", C(=NR')NR'R", $CONHNH_2$, CONHOR', NHCOR', CH_2TNH_2, and CH_2NHCOR'; or R_1 may form, when part of Z or Y, a 5 to 7 membered ring together with the remaining of Y or Z, as per the formulae below



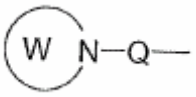


R' and **R"** are selected, each independently, from the group consisting of hydrido, hydroxy, alkyl,

hydroxyalkyl, alkenyl, alkynyl, aryl, arylalkyl, heterocyclyl or heterocyclyl-alkyl;

B is an aromatic 5 or 6 membered ring having from 0 to 3 heteroatoms selected from S, O and N;
A is selected from the group consisting of $-(CH_2)_{m-}$, $-(CH_2)_n-CH=CH-(CH_2)_n-$ and $-(CR_zR_y)_p-$;
$\mathbf{R_z}$ and $\mathbf{R_y}$ are selected, each independently, from hydrido or lower alkyl;
each of the X,Y,Z and B rings being optionally further substituted by one or more $\mathbf{-L-R_2}$ groups, wherein
L represents, each independently, a single bond, an alkylidene group or a divalent group selected from NH, NHCO, CONH, NHCONH, SO_2NH and $NHSO_2$;

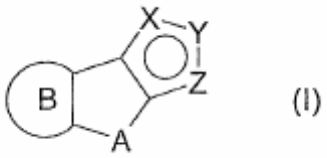
$\mathbf{R_2}$ is, each independently, hydrido, alkyl, 5 to 12 membered mono- or hi-cyclic ring having from 0 to 3 heteroatoms selected from S, O and N, optionally substituted with one or more $-(CH_2)_q-R_3$ groups; or R_2 is a group of formula



W is a 3 to 7 membered ring having one N heteroatom directly linked to Q and from 0 to 2 additional heteroatoms selected from the group consisting of S, SO, SO_2, O, N and NR', wherein R' is as above defined;
Q is a divalent group selected from CO, SO_2 and $(CH_2)_n$;
$\mathbf{R_3}$ is selected, each independently, from the group consisting of alkyl, halogen, CF_3, OCF_3, NO_2, CN, C(=NR')NR'R", OR', SR', OCOR', OCONR'R", $COCF_3$, COR', CO_2R', CONR'R", SO_2R', $SO_2NR'R"$, NR'R", NR'COR', NR'COOR', NR'CONR'R", $NR'SO_2R'$, $NR'SO_2NR'R"$, wherein R' and R" are as above defined;
m is an integer from 1 to 4;

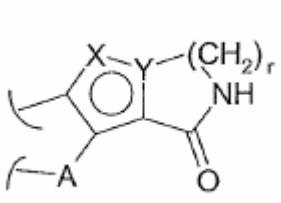
n is, each independently, 0, 1, or 2;
p is 1 or 2;
q is, each independently, 0 or an integer from 1 to 3;
r is an integer from 1 to 3;
or isomers, tautomers, carriers, prodrugs, and pharmaceutically acceptable salts thereof.

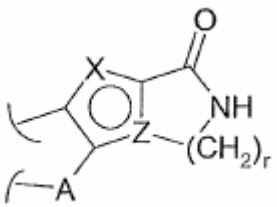
13. A compound represented by formula (I)



(I)

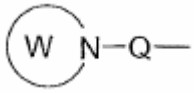
wherein
X, Y and **Z**, being part of an aromatic ring are selected, each independently, from the group consisting of N, NR_1, S, O and CR_1;
$\mathbf{R_1}$ is selected from the group consisting of hydrido, lower alkyl, perfluorinated lower alkyl, heterocyclyl, CN, CO_2R', $COCF_3$, COR', CONR'R", NR'R", C(=NR')NR'R", $CONHNH_2$, CONHOR', NHCOR', CH_2NH_2, and CH_2NHCOR'; or R_1 may form, when part of Z or Y, a 5 to 7 membered ring together with the remaining of Y or Z, as per the formulae below



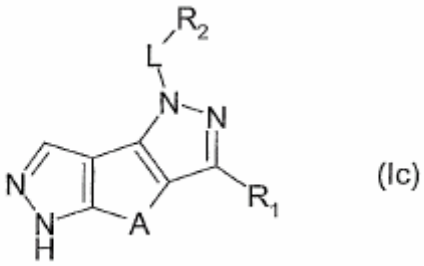


R' and **R"** are selected, each independently, from the group consisting of hydrido, hydroxy, alkyl, hydroxyalkyl, alkenyl, alkynyl, aryl, arylalkyl, heterocyclyl or heterocyclyl-alkyl;
B is an aromatic 5 or 6 membered ring having from 0 to 3 heteroatoms selected from S, O and N;

A is selected from the group consisting of $-(CH_2)_m-$, $-(CH_2)_n-CH=CH-(CH_2)_n-$ and $-(CR_zR_y)_p-$;
$\mathbf{R_z}$ and $\mathbf{R_y}$ are selected, each independently, from hydrido or lower alkyl;
each of the X,Y,Z and B rings being optionally further substituted by one or more **-L-R_2** groups, wherein
L represents, each independently, a single bond, an alkylidene group or a divalent group
selected from NH, NHCO, CONH, NHCONH, SO_2NH and $NHSO_2$;
$\mathbf{R_2}$ is, each independently, hydrido, alkyl, 5 to 12 membered mono- or bi-cyclic ring
having from 0 to 3 heteroatoms selected from S, O and N, optionally substituted with one or more $-(CH_2)_q-R_3$ groups; or R_2 is a group of formula



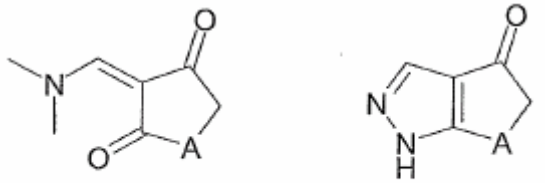
23. A process for preparing a compound of formula (Ic) as defined in claim 16



(Ic)

wherein L and R_2 are as defined in claim 16, R_1 is a group -COOEt or $-CONH_2$, and A is selected from the group consisting of $-CH_2-$, $-CH_2-CH_2-$, -CH=CH- and $-CH_2-C(CH_3)_2-$, which process comprises:

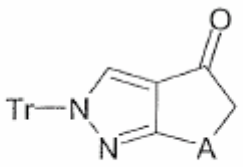
a) reacting the compound (10) with hydrazine dihydrochloride, so as to obtain the compound (11)



(10) (11)

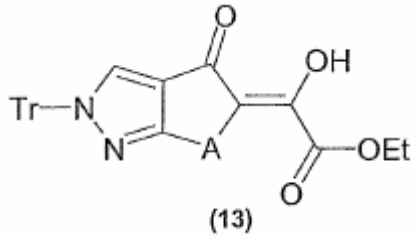
wherein A is as above defined, other than -CH=CH-;

b) reacting the compound (11) with trityl chloride, so as to obtain the compound (12)



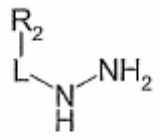
(12)

wherein Tr stands for trityl, and condensing it with oxalyl chloride so as to obtain the compound (13)



(13)

c) reacting the compound (13) with a substituted hydrazine (8)



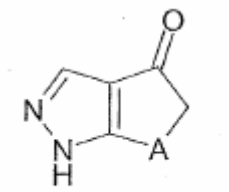
(8)

wherein L and R_2 are as defined in claim 16; so as to obtain a compound of formula (Ic) wherein R_1 is a group -COOEt and A is as above defined except -CH=CH-; and, optionally

d) reacting this latter with ammonium hydroxide so as to obtain the corresponding derivative of formula (Ic) wherein R_1 is $-CONH_2$; and, optionally

e) reacting the compound of formula (Ic) wherein A is $—CH_2-CH_2-$, as obtained in steps c) or d), with a suitable oxidizing agent so as to obtain the corresponding derivative of formula (Ic) wherein A is —CH=CH-.

25. The compound of formula (11)



(11)

wherein A is selected from $-CH_2-$ or $-CH_2-CH_2-$.

29. A product or kit comprising a compound of claim 13 or a pharmaceutical composition thereof as defined in claim 27, and one or more chemotherapeutic agents, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy.

30. A compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 13, for use as a medicament.

31. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 13, in the manufacture of a medicament for treating diseases caused by and/or associated with an altered protein kinase activity.

32. Use according to claim 31 for treating tumors."

II. In its communication dated 7 July 2003, the European Patent Office, acting as an International Searching Authority (ISA), invited the applicant pursuant to Article 17(3)(a) and Rule 40.1 PCT to pay four additional search fees.

Referring to documents (2)(WO 0027822), and (5)(WO 9955335), the ISA found that the protein kinase inhibiting activity of compounds comprising as structural element a pyrazol ring condensed to a carbocyclic ring comprising moiety "A" was known from these prior art documents, which were moreover even novelty-destroying for the claimed subject-matter (ie compounds wherein the B ring condensed to the pyrazol-containing bicyclus is a six-membered ring containing no heteroatom), and inferred from this finding that there was lack of unity.

It considered that as the above-mentioned known structural element was the only common link between all the claimed compounds, the technical problem underlying the present application was only seen in the provision of further compounds as protein kinase inhibitors.

It therefore divided the claimed subject-matter into four different groups of inventions by defining the common structural contribution over said prior art for each of these groups:

Group 1: claims 1 to 7, 12 to 15, 19, 27 to 32 (each partial); 8 to 11, 16 to 18, 20 to 24 (each fully), ie compounds (and subject-matter

referring to these compounds) of formula (Ic), (Ie), (If) or (Ig), the parental system being a bicyclus comprising a pryrazole ring condensed to a carbocyclic ring comprising moiety A and further annelated with a second pyrazole ring.

Group 2: claims 1 to 7, 9, 12 to 14, 19, 27 to 32 (each partial), ie compounds (and subject-matter referring to these compounds) of formula (Ia) or (Id), the parental system being a bicyclus comprising a pryrazole ring condensed to a carbocyclic ring comprising moiety A and further annelated with ring B being a 6-membered ring.

Group 3: claims 1 to 7, 9, 12 to 15, 19, 27 to 32 (each partial), ie compounds (and subject-matter referring to these compounds) of formula (Ia) or (Id), the parental system being a bicyclus comprising a pryrazole ring condensed to a carbocyclic ring comprising moiety A and further annelated with ring B being a 5-membered ring, other than pyrazole or compounds of formula (Ib) wherein ring C2XYZ is not pyrazole.

Group 4: claims 1 to 7, 12, 13, 27 to 32 (each in part), ie further compounds of formula (I) (and subject-matter referring to these compounds) not yet mentioned in groups 1 to 3 having no pyrazole.

The ISA was moreover of the opinion that intermediate compounds of claims 25 and 26 constituted in the present case a separate invention and asked for a fifth additional fee to be paid.

III. With its reply dated 15 July 2003, the applicant paid three additional search fees under protest pursuant to Rule 40.2(c) PCT and requested that inventions group 1 to 4 be searched.

In support of the protest, the applicant merely argued in substance in its "Statement under Rule 40.2(c)" that as general chemical formulae can always be split into sub-classes of compounds by choosing the different meanings of a given substituent, any sort of exercise aimed at identifying subclasses - by virtue of structural features only - had to be regarded as driven by arbitrary assumptions.

It suggested accordingly that groups 1 to 4 should rather be grouped into two groups of inventions, namely group A, relating to compounds of formula (I), wherein at least one of the rings B and/or X-Y-Z comprises a pyrazole moiety, and group B, relating to compounds of formula (I), wherein none of the rings B and X-Y-Z comprises a pyrazole moiety.

IV. In a prior review pursuant to Rule 40.2(e) PCT dated 9 December 2003, the ISA found the invitation to pay additional fees to be justified and invited the applicant to pay the protest fee.

In summary, the Review Panel also considered that, in the light of documents (2) and (5), the claimed subject-matter provided at least four alternative solutions to the problem of the provision of further protein kinase inhibitors defined in the prior art. As these alternatives did not have any special technical features in common (except the known structural element from documents (2) and (5)), it was of the opinion that the ISA was right in its conclusions.

It moreover rejected the appellant's proposal to split the subject-matter of claim 1 into groups A and B because in its view group A was not unitary over the prior art disclosure.

Finally, as to group 4, it submitted that the definition of the compounds contained is this group was misleading because of its definition reciting that the compounds had "no pyrazole moiety", whereas this group in fact also included structures with B as pyrazole and C2XYZ as another 5-membered ring.

It was therefore of the opinion that the refund of one search fee should be ordered as "the applicant had no opportunity to understand the meaning of this invention".

V. With a letter of 23 December 2003, the applicant paid the protest fee according to Rule 40.2(e) PCT.

Reasons for the Decision

1. General requirements for protest proceedings pursuant to Rule 40.2 PCT

1.1 Pursuant to Rule 40.2 PCT, the Board must examine the protest and, to the extent that it finds the protest justified, order the full or partial reimbursement to the applicant of the additional fees.

1.2 According to the established practice of the Boards of Appeal, the examination in protest proceedings has to be carried out in the light of the reasons given by the ISA in its invitation to pay additional fees under Rule 40.2 PCT and the applicant's submissions in support of the protest. The Board cannot investigate of its own motion whether an objection relating to non-unity of invention might be justified for other reasons not considered in the ISA's invitation to pay additional fees (see W 3/93, OJ EPO 1994, 931).

2. In the present case, the ISA's invitation to pay additional fees is based on the findings that documents (2) and (5) disclose all the features of the invention. These conclusions were not contested by the applicant in its above-mentioned "Statement" under Rule 40.2(c) PCT.

Nor did the appellant contest its definition of the problem to be solved by the application over this prior art and the correctness of the distinguishing features which it defined for each of the four groups of structures over said prior art in relation with this problem.

The Board also sees no reason to differ.

2.1 The main argument submitted by the appellant was in fact that as in its view any Markush formula can be split into sub-classes of compounds by choosing the different meanings of a given substituent the four groups defined by the ISA on the basis of structural features were merely the result of arbitrary assumptions.

The Board agrees that a Markush formula can *a priori* always be split into sub-classes of compounds by choosing the different meanings of a given substituent and that such a split when based on structural considerations only would be arbitrary.

This is however not the case here. In fact, as clearly emerges from the invitation to pay additional fees, the groups of inventions have been defined by taking into acccount the problem to be solved over the closest prior art and by looking for a common distinguishing feature over said prior art for each defined group (see pages 1 and 2 under 1. and 2.).

Accordingly, the splitting by the ISA was not based merely on structural considerations, contrary to the appellant's submissions.

On the contrary, the two groups of inventions A and B defined by the appellant appear to be the result of a grouping based solely on structural features since it was made without taking into account of any technical

problem to be solved over the prior art and of any common distinguishing features over said prior art.

2.2 As to the fourth invention, refund of the search fee has been ordered by the review panel and this is therefore not subject to review by the board, irrespective of the fact whether if was well-founded or not.

As regards the remaining search fees paid for the search of the inventions of groups 2 and 3, for the reasons given under 2.1, the Board finds the applicant's protest not justified, so that the protest has to be dismissed.

3. For the sake of completeness, the Board notes that group 1 contains a clerical error and should read: "claims 1-7, 9, 12-15, 19, 27-32 (each partial); 8, 10, 11, 16-18, 20-24 (each fully)".

Order

For these reasons it is decided that:

The protest is dismissed.

The Registrar: The Chairman:

A. Townend U. Oswald